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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/471,622	06/05/95	HUSE W	P-IX-1613

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EXAMINER	
ULM, J	
ART UNIT	**PAPER NUMBER**
1646	28

DATE MAILED: 07/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/471,622	Huse
Examiner	**Group Art Unit**
John Ulm	1646

☒ Responsive to communication(s) filed on *May 2, 2000*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-5, 7, 16-32, 66-75, and 77* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 7, 16-32, 66-75, and 77* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1) Claims 1 to 5, 7, 16 to 32, 66 to 75 and 77 are pending in the instant application. Claims 1, 3, 18, 23 and 24 have been amended as requested by Applicant in Paper Number 26, filed 02 May of 2000.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) 37 C.F.R. § 1.84(U)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by **the same number followed by a capital letter**. The instant application contains a number of partial views of figures on multiple sheets which are intended to be combined to form complete views. For example, the figures labeled 2-1 and 2-2 should be labeled 2A and 2B. Once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly. If, for example, Figure 2 is divided into Figures 2A and 2B then the Brief Description and all references to this figure in the specification must refer to Figures 2A and/or 2B.

5) Claims 1 to 5, 7 and 77 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for those reasons of record in

section 6 of Paper Number 24. These claims require the construction of a DNA encoding a fusion protein comprising the gene VIII gene product of a filamentous bacteriophage, wherein the fusion protein is expressed on the surface of a cell. The gene VIII gene product of a filamentous bacteriophage is a coat protein which is not naturally expressed on the surface of any cell. As indicated in the text in the third paragraph on page 316 of the Wilson et al. publication, which was cited by Applicant in traversal of this rejection, the gene VIII product pVIII is expressed in the **inner membrane** of a host cell, with the C-terminal anchored in the inner membrane and the N-terminal **in the periplasm**. No portion of pVIII is expressed **on the surface** of the host cell. To become expressed **on the surface** of a Gram negative host cell would require that protein to be transported across the inner membrane of that cell without becoming embedded therein as pVIII normally is, across the periplasmic space and then across the outer membrane into which it would have to become embedded or attached. Because the gene VIII gene product of a filamentous bacteriophage is not normally transported to the surface of a bacterial host expressing it a practitioner of the art would require substantial technical guidance to practice the invention as claimed. The instant specification is completely devoid of any of that technical guidance that would be needed by a practitioner of the art to obtain the expression of a viral coat protein on the surface of a bacterial cell as required by these claims. The assertions in the specification that gene VIII fusions can be expressed on the surface of a cell, in the absence of guidance, working examples or the identification of prior art describing the expression of an analogous viral coat protein on a cell, constitutes nothing more than an invitation to experiment. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of

Genentec, Inc, v. Novo Nordisk, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not following the guidance presented therein and produce the claimed composition without first making a substantial inventive contribution. Applicant's argument that pVIII is anchored to the cell surface via filamentous phage is not persuasive. Filamentous phage are extruded from the cell and are not retained on the surface of that cell. One of ordinary skill would not equivocate the expression of a protein on the surface of a virus which is extruded from a cell with the expression of that protein on the surface of that cell.

6) Claims 1 to 4, 7, 16 to 19, 21 to 29, 31, 32, 66 to 75 and 77 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is not enabling for the production of first and second DNA sequences encoding the functional portions of any "heteromeric receptor" protein other that the variable heavy and variable light chains of an antibody or T cell receptor molecule, or for the production of a vector comprising sequences "necessary" for the expression of any other "heteromeric receptor" protein on the surface of a filamentous bacteriophage for those reasons of record in section 7 of Paper Number 24. Applicant asserts that antibodies are receptors. Merriam

Webster's Collegiate Dictionary defines a receptors as "a chemical group or molecule (as a protein) on the cell surface or in the cell interior that has an affinity for a specific chemical group, molecule, or virus". Applicant is advised that the art of molecular biology recognizes a receptor as a membrane bound protein or protein complex which comprises one or more extracellular domains that reversibly bind a ligand without altering the structure of that ligand upon dissociation, one or more transmembrane domains which span the cellular membrane and serve to anchor the receptor therein, and one or more cytoplasmic domains which induce a physiological response in a cell as a consequence of the bind of a ligand to the extracellular domain(s) of that receptor. If the ligand is chemically altered by its interaction with a protein, then the protein in question is not a receptor, it is an enzyme. An antibody is expressed neither at a cell surface or in the cell interior. Therefore, the guidance provided in the instant specification for the expression of antibody components on the surface of filamentous bacteriophage would not be accepted by one of ordinary skill in the art of molecular biology as being applicable to receptor proteins because **antibodies are not receptors** in any art-recognized sense of the word.

The text in the second paragraph on page 5 of the instant specification indicates that the term "heteromeric receptors" encompasses "transmitter receptors". The Nakanishi publication (SCIENCE 258:597-603, 23 Oct. 1992) is being cited because it gives a brief overview of the structure and function of the large family of proteins which are known in the art as ionotropic neurotransmitter receptors. As indicated by the text on page 598 of this reference and illustrated by Figure 2 therein, members of the ligand-gated ion channel family, which includes receptors for the neurotransmitter acetylcholine, glutamate, glycine and γ-aminobutyric acid, have a complex structure comprising five

protein subunits wherein each subunit comprises four transmembrane spanning regions. This reference exemplifies the state of the art at the time it was published and shows that "transmitter receptors" are either members of the G protein-coupled receptor family, which are not "heteromeric", and ionotropic receptors which are composed of multiple subunits having complex structures comprising multiple transmembrane domains which only function within the context of a cell membrane. Because these heterologous receptors are only known to function as pentameric complexes within the context of a cellular membrane, one would not accept Applicant's proposition that such heterologous "transmitter receptors" could be functionally expressed on the surface of a filamentous bacteriophage, as taught by the instant specification. Further, because ligand-gated ion channels have absolutely no structural or functional similarities to the antibody molecules which have been employed in the examples of the instant specification, an artisan would not view the guidance and results described in the instant specification to be predictive any results which might be achieved if one attempted to functionally express an ionotropic neurotransmitter receptor on the surface of a bacteriophage.

The only expression system which is described in the instant specification in such clear and concise detail that an artisan could practice it is the expression of the VH and VL chains of an antibody on the surface of a filamentous bacteriophage and the expression of a single chain antibody consisting of a VH chain joined to a VL chain on the surface of a filamentous bacteriophage was a practice that was well known in the art prior to the making of the instant invention.

7) Claims 70 and 75 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. These claims are vague and indefinite in the recitation of the limitation "has substantially the same sequence" because it is not possible to determine at what point a similar sequence would cease to be substantially the same as a reference sequence. Specifically, one can not determine the metes and bounds of these claims in view of this limitation for those reasons of record.

8) Claims 16 to 32 and 68 to 75 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 33 and 68 to 75 of related Application No. 08/470,297, now Patent Number 6,027,933, for those reasons of record in section 8 of Paper Number 12. Any further response by Applicant which does not resolve this issue will be held non-responsive.

9) Claims 1 to 5, 7, and 16 to 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 8, 16 to 21 and 23 to 33 of copending Application Number 08/349,131, now claims 1 to 32 of U.S. Patent Number 5,871,974, for those reasons of record in section 9 of Paper Number 12. The filing of a terminal disclaimer after the issuance of this final rejection would not be considered timely since this issue has been of record throughout the prosecution of the instant application..

10) Claims 66 to 75 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Huse et al. publication (Science 246:1275-1281, 1989) in view of the Ladner et al. publication (WO 88/06630, 1988) and the Ladner et al. patent (5,223,409) essentially for those reasons of record in section 14 of Paper Number 12. Applicant is advised that the limitations "capable of being operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor" , "necessary for the coexpression of two or more inserted DNA sequences encoding which form heteromeric receptors", and "capable of being linked" are not distinguishing because "functional

statements therein do not limit article claims", (in re Hutchison, 69 USPQ 138 (CCPA 19467)). Therefore, claims 66 and 71 encompasses any vector comprising two copies of a gene encoding a filamentous bacteriophage coat protein since any such vector will function in the capacity recited in these claims. The Ladner et al. patent has been relied upon to demonstrate that the express limitations of claims 66 to 75, which require two copies of gene VIII that differ from one another in nucleotide sequence, was expressly suggested by the art at the time of the instant invention. Example I beginning in column 105 of the Ladner et al. patent taught the construction of an M13 cloning vector containing two genes encoding gVIII. The first gene is employed to obtain the expression of a potential binding protein on the surface of M13 bacteriophage as a gVIII fusion, and the second provides the wild-type gene VIII protein which is needed to produce structurally viable bacteriophage, as indicated by the text in lines 13 to 24 in column 113. The text in lines 27 to 31 of column 106 expressly taught that "[s]everal silent codon changes were made" in the chimeric gVIII gene "so that the longest segment that is identical to wild-type gene VIII is minimized so that genetic recombination with the co-existing gene VIII is unlikely". Applicant has neither identified that material limitation which distinguishes the claimed vector from that of Ladner et al. or explained why one of ordinary skill in the art could not have produced the vector that was suggested by Ladner et al. by following those routine practices that were described in that patent.

11) Applicant's arguments filed 02 May of 2000 have been fully considered but they are not persuasive.

12) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kuntz can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800